AMENDMENTS TO THE SPECIFICATION

Please amend the specification as shown, without prejudice or disclaimer.

At page 16 of the substitute specification submitted May 10, 2005, please replace the paragraph beginning at line 26 with the following amended paragraph:

Amylin agonist analogues useful in the methods of this application include amylin agonist analogues having the following amino acid sequence [SEQ ID NO:31]:

$^{1}A_1$-X-Asn-Thr-^{5}Ala-Thr-Y-Ala-Thr-^{10}Gln-Arg-Leu-B_1-
Asn-^{15}Phe-Leu-C_1-D_1-E_1-$^{20}F_1$-G_1-Asn-H_1-Gly-$^{25}I_1$-J_1-
Leu-K_1-L_1-^{30}Thr-M_1-Val-Gly-Ser-^{35}Asn-Thr-Tyr-Z

wherein A_1 is hydrogen Lys, Ser, Ala, des-α-amino Lys, or acetylated Lys; B_1 is Ala, Ser or Thr; C_1 is Val, Leu or Ile; D_1 is His or Arg; E_1 is Ser or Thr; F_1 is Ser, Thr, Gln or Asn; G_1 is Asn, Gln or His; H_1 is Phe, Leu or Tyr; I_1 is Ala or Pro; J_1 is Ile, Val, Ala or Leu; K_1 is Ser, Pro, Leu, Ile or Thr; L_1 is Ser, Pro or Thr; M_1 is Asn, Asp or Gln; X and Y are independently selected residues having side chains which are chemically bonded to each other to form an intramolecular linkage; and Z is hydroxy, amino, alkylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, alkyloxy, aryloxy or aralkyloxy; provided that (a) when A_1 is Lys, B_1 is Ala, C_1 is Val, D_1 is His, E_1 is Ser, F_1 is Ser, G_1 is Asn, H_1 is Phe, I_1 is Ala, J_1 is Ile, K_1 is Ser, L_1 is Ser, and M_1 is Asn [SEQ ID NO:46]; (b) when A_1 is Lys, B_1 is Ala, C_1 is Ile, D_1 is Arg, E_1 is Ser, F_1 is Ser, G_1 is Asn, H_1 is Leu, I_1 is Ala, J_1 is Ile, K_1 is Ser, L_1 is Pro, and M_1 is Asn [SEQ ID NO:47]; (c) when A_1 is Lys, B_1 is Ala, C_1 is Val, D_1 is Arg, E_1 is Thr, F_1 is Ser, G_1 is Asn, H_1 is Leu, I_1 is Ala, J_1 is Ile, K_1 is Ser, L_1 is Pro, and M_1 is Asn [SEQ ID NO: 48]; (d) when A_1 is Lys, B_1 is Ala[[.]], C_1 is Val, D_1 is Arg, E_1 is Ser, F_1 is Ser, G_1 is Asn, H_1 is [[Lea]] Leu, I_1 is Pro, J_1 is Val, K_1 is Pro, L_1 is Pro, and M_1 is Asn [SEQ ID NO: 41]; (e) when A_1 is Lys, B_1 is Ala, C_1 is Val, D_1 is His, E_1 is Ser, F_1 is Asn, G_1 is Asn, H_1 is Leu, I_1 is Pro, J_1 is Val, K_1 is Ser, L_1 is Pro and M_1 is Asn [SEQ ID NO: 43]; or (f) when A_1 is Lys, B_1 is Thr, C_1 is Val, D_1 is Arg, E_1 is Ser, F_1 is Ser, G_1 is His, H_1 is Leu, I_1 is Ala, J_1 is Ala, K_1 is Leu, L_1 is Pro and M_1 is Asp [SEQ ID

NO: 49]; then one or more of any of A_1 to M_1 is not an L-amino acid and Z is not amino ~~[SEQIDNO: 31]~~.

At page 22 of the substitute specification submitted May 10, 2005, please replace the paragraph beginning at line 6 with the following amended paragraph:

Assays of biological activity of amylin agonists, including amylin agonist analogue preparations in the soleus muscle are performed using previously described methods (Leighton, B. and Cooper, G. J. S., *Nature,* 335:632-635 (1988); Cooper, G. J. S., *etal, Proc. Natl Acad. Sci. USA* 85:7763-7766 (1988)). In summary, amylin agonist activity is assessed by measuring the inhibition of insulin-stimulated glycogen synthesis in soleus muscle. Amylin antagonist activity is assessed by measuring the resumption of insulin-stimulated glycogen synthesis in the presence of 100 nM rat amylin and an amylin antagonist. Concentrations of peptide dissolved in carrier-free buffers are determined by quantitative amino acid analysis, as described therein. The ability of compounds to act as agonists in this assay is determined by measuring EC_{50} values. Standard errors are determined by fitting of sigmoidal dose response curves using a four parameter logistic equation (De Lean, A., Munson, P. J., Guardabasso, V. and Rodbard, D. (1988) *ALLFIT,* Version 2.7, National Institute of Child Health and Human Development, N.I.H. Bethesda, Md., 1 diskette). A number of amylin agonists have been characterized using these biological assays. The compounds $^{18}Arg^{25,28}Pro$ -h-amylin [SEQ ID NO:3], $des^{1}Lys^{18}Arg^{25,28}Pro$ -h-amylin [SEQ ID NO:6], $^{18}Arg^{25,28,29}Pro$-h-amylin [SEQ ID NO:8], $des\text{-}^{1}Lys^{18}Arg^{25,28,29}Pro$ -h-amylin [SEQ ID [[~~NO:10~~]] NO:9], $^{25,28,29}Pro$-h-amylin [SEQ ID NO:1], $des\text{-}^{1}Lys^{25,28,29}Pro$-h-amylin [SEQ ID NO: 10], and $^{25}Pro^{26}Val^{25,28}Pro$-h-amylin [SEQ ID NO:7] were all found to compete with amylin in the receptor binding assay. These compounds have negligible antagonist activity as measured by the soleus muscle assay and were shown to act as amylin agonists. Similar results were obtained with other agonist compounds listed above.

At page 29 of the substitute specification submitted May 10, 2005, please replace the paragraph beginning at line 20 with the following amended paragraph:

The effective daily anti-emptying dose of the compounds including $^{18}Arg^{25,28}Pro$-h-amylin [SEQ ID NO:3], des-$^{1}Lys^{18}Arg^{25,28}Pro$-h-amylin [SEQ ID NO:6], $^{18}Arg^{25,28,29}Pro$-h-amylin [SEQ ID NO:8], des-$^{1}Lys^{18}Arg$-$^{25,28,29}Pro$-h-amylin [SEQ ID [[~~NO:10~~]] NO:9], $^{25,28,29}Pro$-h-amylin [SEQ ID NO:1], des-$^{1}Lys^{25,28,29}Pro$-h-amylin [SEQ ID NO:10], and $^{25}Pro^{26}Val^{25,28}Pro$-h-amylin [SEQ ID NO:7], will typically be in the range of 0.01 or 0.03 to about 5 mg/day, preferably about 0.01 or 0.5 to 2 mg/day and more preferably about 0.01 or 0.1 to 1 mg/day, for a 70 kg patient, administered in a single or divided doses. The exact dose to be administered is determined by the attending clinician and is dependent upon where the particular compound lies within the above quoted range, as well as upon the age, weight and condition of the individual. Administration should begin at the first sign of symptoms or shortly after diagnosis of diabetes mellitus. Administration may be by injection, preferably subcutaneous or intramuscular. Orally active compounds may be taken orally, however dosages should be increased 5-10 fold.

At page 43 of the substitute specification submitted May 10, 2005, please replace the paragraph beginning at line 3 with the following amended paragraph:

Solid phase synthesis of this amylin analogue using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. ^{2}Asp and ^{7}Lys were introduced with Boc-^{2}Asp(Fmoc)-OH and Boc-^{7}Lys(Fmoc)-OH. Following selective side-chain deprotection with piperidine, the side-chain to side-chain (^{2}Asp-^{7}Lys) cyclization was carried out using benzotriazol-lyl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate(BOP reagent). Cyclization was as described in Di Maio, J., *et al.*, *J. Med. Chem.*, 33:661-667 (1990); and Felix, A.M., *et al.*, *Int. J. Pept. Prot. Res.*, 32:441 (1988). The ^{2,7}cyclo-[^{2}Asp,^{7}Lys]amylin-MBHA-resin obtained after cyclization was cleaved with liquid HF in the presence of dimethylsulfide and anisole. The ^{2,7}cyclo-[^{2}Asp,^{7}Lys]-h-amylin [SEQ ID NO:32] was purified by preparative HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. FAB mass spec: (M+l)/e=3925.

At page 44 of the substitute specification submitted May 10, 2005, please replace the paragraph beginning at line 3 with the following amended paragraph:

Solid phase synthesis of ^{1}Ala-h-amylin [SEQ ID NO:33] using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected ~~cystenes~~ cysteines with thallium [[(M)]] (III) trifluoroacetate in ~~trifluoroaceue~~ trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The ^{1}Ala-h-amylin [SEQ ID NO:33] was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion, FAB mass spec: $(M+H)^{+}$=3,847.

At page 44 of the substitute specification submitted May 10, 2005, please replace the paragraph beginning at line 15 with the following amended paragraph:

Solid phase synthesis of ^{1}Ser-h-amylin [SEQ ID NO:34] using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The ^{1}Ser-h-amylin [SEQ ID NO:34] was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^{+}$=3,863.

At page 44 of the substitute specification submitted May 10, 2005, please replace the paragraph beginning at line 27 with the following amended paragraph:

Solid phase synthesis of this analogue of human amylin using ~~methylbenzhydrylamine~~ methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The ^{29}Pro-h-amylin [SEQ ID NO:35] was purified by preparative HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^{+}$=3916.

At page 45 of the substitute specification submitted May 10, 2005, please replace the paragraph beginning at line 10 with the following amended paragraph:

Solid phase synthesis of ^{25,28}Pro-h-amylin [SEQ ID NO:36] using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The ^{25,28}Pro-h-amylin [SEQ ID NO:36] was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^{+}$=3,939.

At page 45 of the substitute specification submitted May 10, 2005, please replace the paragraph beginning at line 22 with the following amended paragraph:

Solid phase synthesis of des-^{1}Lys^{25,28}Pro-h-amylin [SEQ ID NO:37] using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried

out by standard peptide synthesis methods. The 2,7-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected ~~cystemes~~ cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The des-^{1}Lys^{25,28}Pro-h-amylin [SEQ ID NO:37] was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^{+}$=3,811.

At page 48 of the substitute specification submitted May 10, 2005, please replace the paragraph beginning at line 27 with the following amended paragraph:

Solid phase synthesis of this h-amylin analogue using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection is carried out by standard peptide synthesis methods, and the ^{2,7}-[disulfide]amylin-MBHA-resin obtained by treatment with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization is achieved, the resin and side chain protecting groups are cleaved with liquid HF in the presence of dimethylsulfide and anisole. The des-^{1}Lys^{25}Pro^{26}Val^{28,29}Pro-h-amylin [SEQ ID NO:38] is then purified by preparative HPLC.

At page 49 of the substitute specification submitted May 10, 2005, please replace the paragraph beginning at line 7 with the following amended paragraph:

Solid phase synthesis of this amylin analogue using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection is carried out by standard peptide synthesis methods. (D)-^{11}Arg is introduced with Boc-(D)-^{11}Arg(Mtr)-OH. The ^{2,7}-[disulfide]amylin-MBHA-resin, obtained by treatment with thallium (III) trifluoroacetate in trifluoroacetic acid, is cyclized and the resin and side chain protecting groups are cleaved with liquid HF in the presence of dimethylsulfide and anisole. The [(D)-^{11}Arg]-amylin [SEQ ID NO:39] is then purified by preparative HPLC.